



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of : Heinz-Gerd KLAES) Art Unit : To be assigned
Serial No. : 10/809,250) Examiner : To be assigned
Confirmation No. : To be assigned
Filed : March 25, 2004
For : PHARMACEUTICAL COMPOSITION OF ANTIVIRAL
AGENTS
Docket No. : 1/1477

Commissioner for Patents
Washington, D.C. 20231

CLAIM FOR FOREIGN PRIORITY UNDER 35 U.S.C. § 119

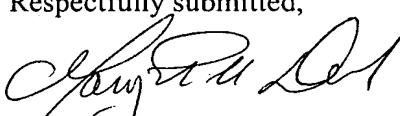
Sir:

Applicants hereby claim for the above captioned application priority of the following foreign application(s):

Foreign Priority Number:03029526.5, dated December 20, 2003, Foreign Priority Number 03016226.7, dated July 17, 2003 and Foreign Priority Number 03006996.7, dated March 27, 2003.

A certified copy of the above foreign application(s) is(are) enclosed.

Respectfully submitted,


Mary-Ellen M. Devlin
Attorney for Applicant(s)
Reg. No. 27,928

Patent Department
Boehringer Ingelheim Corp.
900 Ridgebury Road
P.O. Box 368
Ridgefield, CT. 06877
Tel.: (203) 798-4866

I hereby certify that this correspondence is being deposited with the U.S. Postal Service as first class mail in an envelope addressed to:

Commissioner for Patents
Washington, DC 20231

on April 28, 2004


By: Mary-Ellen M. Devlin
Reg. No. 27,928



THIS PAGE BLANK (USPTO)



Europäisches
Patentamt

European
Patent Office

Office européen
des brevets

Bescheinigung

Certificate

Attestation

Die angehefteten Unterlagen stimmen mit der ursprünglich eingereichten Fassung der auf dem nächsten Blatt bezeichneten europäischen Patentanmeldung überein.

The attached documents are exact copies of the European patent application described on the following page, as originally filed.

Les documents fixés à cette attestation sont conformes à la version initialement déposée de la demande de brevet européen spécifiée à la page suivante.

Patentanmeldung Nr. Patent application No. Demande de brevet n°

03029526.5

Der Präsident des Europäischen Patentamts;
Im Auftrag

For the President of the European Patent Office

Le Président de l'Office européen des brevets
p.o.

R C van Dijk

THIS PAGE BLANK (USPTO)



Anmeldung Nr:
Application no.: 03029526.5
Demande no:

Anmeldetag:
Date of filing: 20.12.03
Date de dépôt:

Anmelder/Applicant(s)/Demandeur(s):

Boehringer Ingelheim International GmbH
Binger Strasse 173
55216 Ingelheim am Rhein
ALLEMAGNE

Bezeichnung der Erfindung/Title of the invention/Titre de l'invention:
(Falls die Bezeichnung der Erfindung nicht angegeben ist, siehe Beschreibung.
If no title is shown please refer to the description.
Si aucun titre n'est indiqué se referer à la description.)

Pharmaceutical composition of antiviral agents

In Anspruch genommene Priorität(en) / Priority(ies) claimed /Priorité(s)
revendiquée(s)
Staat/Tag/Aktenzeichen/State>Date/File no./Pays/Date/Numéro de dépôt:

Internationale Patentklassifikation/International Patent Classification/
Classification internationale des brevets:

A61K31/00

Am Anmeldetag benannte Vertragstaaten/Contracting states designated at date of
filing/Etats contractants désignées lors du dépôt:

AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LU MC NL
PT RO SE SI SK TR LI



20. Dez. 2003

PHARMACEUTICAL COMPOSITION OF ANTIVIRAL AGENTS

FIELD OF THE INVENTION

The present invention relates to a pharmaceutical composition
5 useful for the treatment of viral infections comprising
nevirapine and at least one antiviral active compound of
formula (I). Furthermore the present invention relates to a
use of nevirapine in combination or alternation with a
compound of formula (I) in the prophylaxis or treatment of a
10 viral infection in a patient. The present invention also
relates to a use of nevirapine in combination with a compound
of formula (I) for the manufacture of a medicament for the
prophylaxis or treatment of a viral infection in a patient. In
addition the present invention relates to a kit of parts and
15 to a manufacture for the prophylaxis or treatment of a viral
infection in a patient.

BACKGROUND OF THE INVENTION

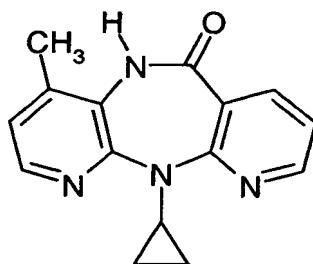
20 Human immunodeficiency virus (HIV) is recognized as the
causative agent in AIDS.

Current therapies for HIV infection focus on inhibiting the
activity of viral enzymes which are essential to the life
25 cycle of the virus. The agents that are presently in use fall
mainly into three classes, designated Nucleoside Reverse
Transcriptase Inhibitors (NRTIs), Non-nucleoside Reverse
Transcriptase Inhibitors (NNRTIs), and Protease Inhibitors
(PIs). Presently, combination therapies, i.e. the selection of
30 two or more antiretroviral agents taken together to make up a
"drug cocktail," are the preferred treatment for HIV
infection. Combination therapies have been shown to reduce the
incidence of opportunistic infections and to increase survival
time. Typically, the drug cocktail combines drugs from
35 different classes, so as to attack the virus at several stages
in the replication process. This approach has been shown to

reduce the likelihood of the development of virus forms that are resistant to a given drug or class of drugs.

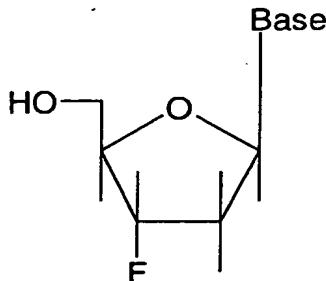
Treatment failure with rebound of the amount of HIV which can
5 be measured in the blood is common for patients treated with
combination antiretroviral regimens. Resistance to the drugs
in the drug regimen develops as the virus replicates in the
presence of these drugs. Because of structural similarities of
the drugs within an antiretroviral class, cross resistance is
10 commonly seen to the other members of that class (for example
virologic failure on a regimen containing an NNRTI will lead
to cross resistance to the other first generation NNRTI
agents). As patients experience repeated virologic failure on
antiretroviral combination therapy, their viruses develop
15 broad multi-class antiretroviral drug resistance which limits
the effectiveness of the next round of antiretroviral therapy.
Many highly treatment experienced patients have been exposed
to all three classes of antiretroviral drugs and cannot obtain
two active drugs to form the core of a new, effective
20 antiretroviral drug regimen.

Nevirapine (Viramune®) is a non-nucleoside inhibitor of HIV reverse transcriptase, which is useful in the treatment of HIV infection in humans. The chemical name for nevirapine is 11-cyclopropyl-5,11-dihydro-4-methyl-6H-dipyrido[3,2-b:2',3'-e][1,4]diazepin-6-one. Its structural formula is:



30 The earliest known synthesis of nevirapine, by Hargrave et al., is described in US Patent 5,366,972.

Furthermore compounds of the formula (I)

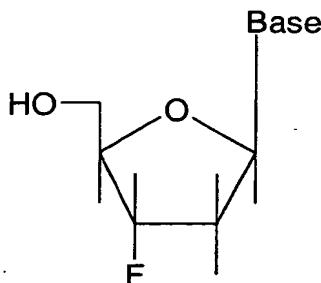


wherein Base is selected from the group consisting of thymine,
5 cytosine, adenine, guanine, inosine, uracil, 5-ethyluracil and
2,6-diaminopurine, or a pharmaceutically acceptable salt or
prodrug thereof, are described in the WO 88/00050 and
WO 91/01137 for the therapeutic and prophylactic control and
treatment of AIDS, HIV infections, hepatitis B virus (HBV)
10 infections and retrovirus infections in animals and man. These
nucleoside compounds are transformed by cells or enzymes to
triphosphates which inhibit the reverse transcriptase of
retrovirus as well as the activity of DNA dependent polymerase
of hepatitis B virus.
15 Combinations of nevirapine with at least one compound of the
formula (I) which exhibit potent therapeutic activity against
HIV and HBV would greatly aid in the development of new
combination therapy against human retroviral (HRV) infections
20 and HBV.

SUMMARY OF THE INVENTION

In one aspect, the present invention provides a novel
pharmaceutical composition useful for the treatment or
25 prophylaxis of viral infections comprising nevirapine and at
least one antiviral active compound of formula (I)

- 4 -

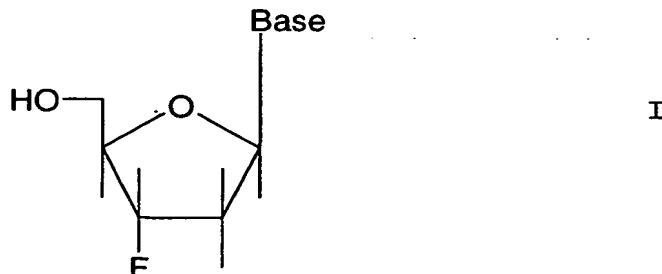


wherein Base is selected from the group consisting of thymine, cytosine, adenine, guanine, inosine, uracil, 5-ethyluracil and 2,6-diaminopurine, or a pharmaceutically acceptable salt or
5 prodrug thereof.

The pharmaceutical compositions of the present invention are useful in therapy, in particular as antivirals, especially in the treatment or prophylaxis of human retroviral (HRV)
10 infections.

In a second aspect, there is provided a use of nevirapine in combination or alternation with at least one antiviral active compound of formula (I)

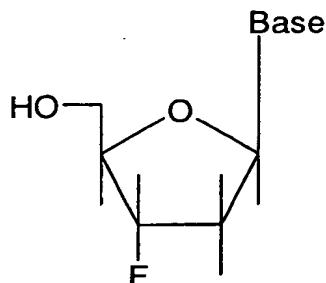
15



wherein Base is selected from the group consisting of thymine, cytosine, adenine, guanine, inosine, uracil, 5-ethyluracil and 2,6-diaminopurine, or a pharmaceutically acceptable salt or
20 prodrug thereof, in the prophylaxis or treatment of a viral infection in a patient.

In a third aspect, there is provided a use of nevirapine in combination with at least one antiviral active compound of
25 formula (I)

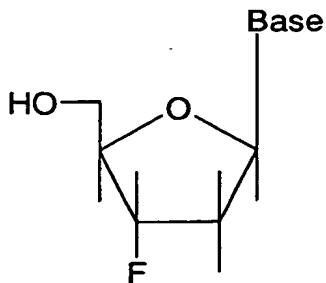
- 5 -



wherein Base is selected from the group consisting of thymine,
cytosine, adenine, guanine, inosine, uracil, 5-ethyluracil and
5 2,6-diaminopurine, or a pharmaceutically acceptable salt or
prodrug thereof, for the manufacture of a medicament for the
prophylaxis or treatment of a viral infection in a patient.

In a fourth aspect of this invention, there is provided a kit
10 of parts for the prophylaxis or treatment of a viral infection
in a patient, comprising

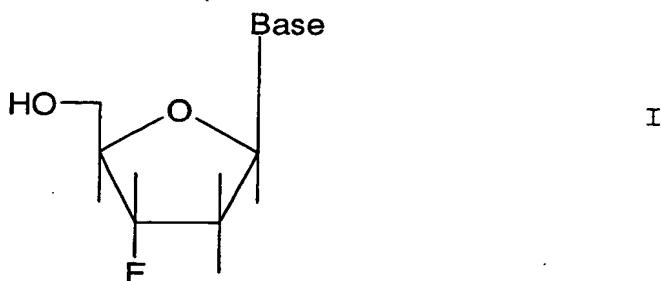
- (a) a first containment containing a pharmaceutical composition comprising nevirapine and at least one pharmaceutically acceptable carrier, and
- 15 (b) a second containment containing a pharmaceutical composition comprising an antiviral active compound of formula (I)



20 wherein Base is selected from the group consisting of thymine,
cytosine, adenine, guanine, inosine, uracil, 5-ethyluracil and
2,6-diaminopurine, or a pharmaceutically acceptable salt or
prodrug thereof, and at least one pharmaceutically acceptable
carrier.

In a fifth aspect of this invention, there is provided a manufacture comprising nevirapine and at least one antiviral active compound of formula (I)

5



wherein Base is selected from the group consisting of thymine, cytosine, adenine, guanine, inosine, uracil, 5-ethyluracil and 2,6-diaminopurine, or a pharmaceutically acceptable salt or 10 prodrug thereof, for use in combination or alternation in the prophylaxis or treatment of a viral infection in patient.

With the combination of nevirapine and a compound of the formula (I) according to this invention, including its use in 15 prophylaxis and treatment, the person skilled in the art can achieve an advantageous therapeutic effect to inhibit viral replication, especially of human retrovirus (HRV) and HBV, in particular of multiresistant HIV. In most cases, the enhanced therapeutic effect is not attainable by administration of 20 either agent alone. In a preferred but not necessary embodiment, the effect of administration of nevirapine and the compound of formula (I) in combination or alternation is synergistic. Even though a combination exhibits additive and not synergistic effects, the combination can still provide an 25 effect that is different from the separate administration of the two agents. For example, the biodistribution, pharmacokinetics, cytotoxic effects or metabolism of one can be affected by the other.

Further aspects of the present invention become apparent to the one skilled in the art from the following detailed description and examples.

5 **DEFINITIONS**

The term "pharmaceutically acceptable salt" means a salt of the corresponding compound which is, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response, and the like, commensurate with a reasonable benefit/risk ratio, generally water or oil-soluble or dispersible, and effective for their intended use. The term includes pharmaceutically-acceptable acid addition salts and pharmaceutically-acceptable base addition salts. Lists of suitable salts are found in, e.g., S.M. Birge et al., J. Pharm. Sci., 1977, 66, pp. 1-19, which is hereby incorporated by reference in its entirety.

As used herein, the term "treatment" means the administration of the antivirally active compounds according to this invention in combination or alternation according to the present invention to alleviate or eliminate symptoms of the viral infection and/or to reduce viral load in a patient.

As used herein, the term "prevention" or "prophylaxis" means the administration of the antivirally active compounds according to this invention in combination or alternation according to the present invention post-exposure of the individual to the virus but before the appearance of symptoms of the disease, and/or prior to the detection of the virus in the blood.

As used herein, the term "human retrovirus" (HRV) includes human immunodeficiency virus type I, human immunodeficiency virus type II, or strains thereof, as well as human T cell

- 8 -

leukemia virus 1 and 2 (HTLV-1 and HTLV-2) or strains apparent to one skilled in the art, which belong to the same or related viral families and which create similar physiological effects in humans as various human retroviruses.

5

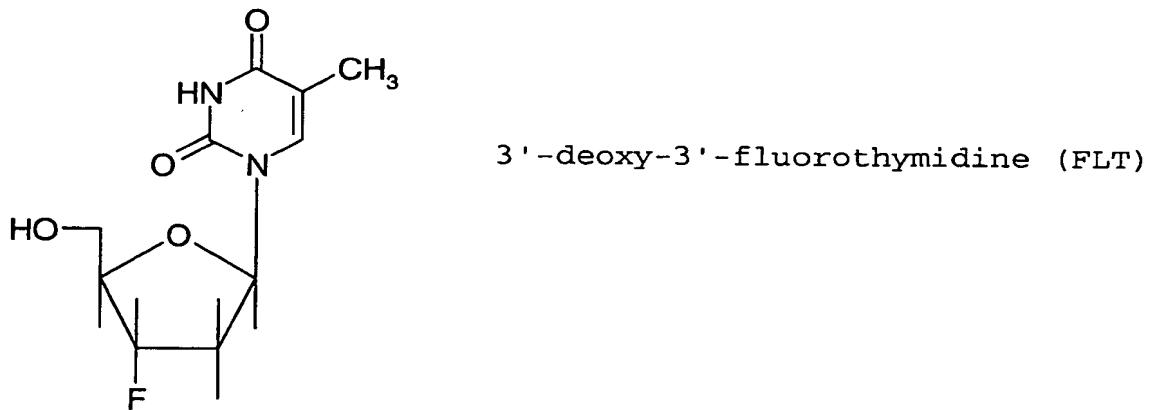
DETAILED DESCRIPTION OF THE INVENTION

The virally active agents according to this invention may be in either free form or in protected form at one or more of the remaining (not previously protected) carboxyl, amino, hydroxy, 10 or other reactive groups. The protecting groups may be any of those known in the art. Furthermore, the virally active agents according to this invention may also be used as in form of their pharmacologically acceptable salts and/or hydrates.

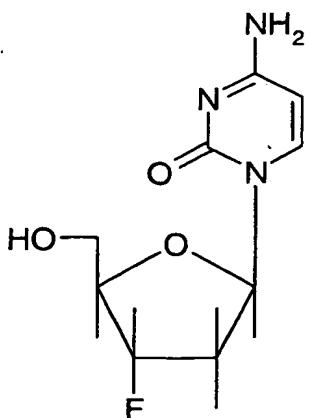
15 According to the first aspect of this invention, there is provided a novel pharmaceutical composition useful for the treatment of viral infections comprising nevirapine and at least one antiviral active compound of formula (I), or a pharmaceutically acceptable salt or prodrug thereof.

20

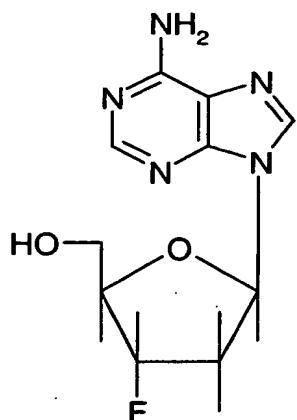
The following known compounds constitute part of the invention as preferred compounds of the formula (I) to be combined with nevirapine:



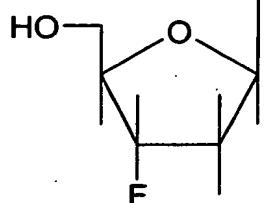
- 9 -



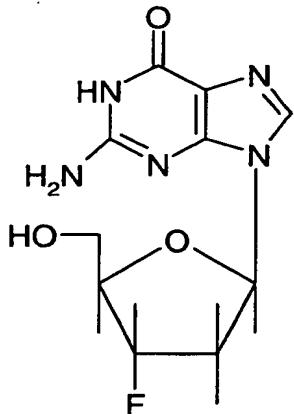
2',3'-dideoxy-3'-fluorocytidine



2',3'-dideoxy-3'-fluoroadenosine



2',3'-dideoxy-3'-fluoroguanosine
(FLG)



including pharmaceutically acceptable salts and prodrugs of the compounds listed above.

- 5 Preferred prodrugs of FLG are described in WO 99/09031 and WO 99/41268, which documents in their entirety are incorporated herein by reference.

- 10 -

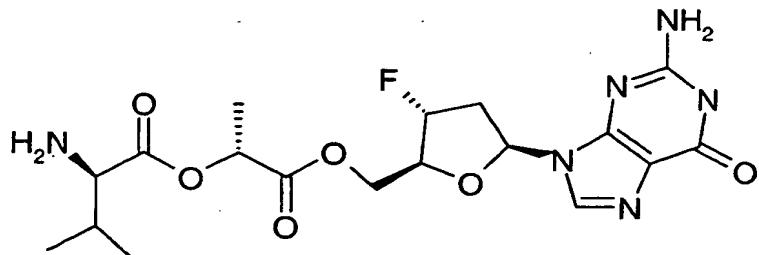
The most preferred compound of the formula (I) to be combined with nevirapine according to the aspects of this invention is selected from the group consisting of

(a) 3'-deoxy-3'-fluorothymidine, or a pharmaceutically acceptable salt or prodrug thereof, and

5 (b) 2',3'-dideoxy-3'-fluoroguanosine (FLG), or a pharmaceutically acceptable salt or prodrug thereof, in particular 3'-deoxy-3'-fluoro-5-O-[2-(L-valyloxy)-propionyl]guanosine, or a pharmaceutically acceptable salt thereof.

10 The compound of the formula (I) is very most preferably selected from the group consisting of 3'-deoxy-3'-fluorothymidine and 3'-deoxy-3'-fluoro-5-O-[2-(L-valyloxy)-propionyl]guanosine, including pharmaceutically acceptable salts thereof.

15 3'-deoxy-3'-fluoro-5-O-[2-(L-valyloxy)-propionyl]guanosine is a preferred prodrug of FLG and can be depicted by the
20 following structure



25 The synthesis of 3'-deoxy-3'-fluoro-5-O-[2-(L-valyloxy)-propionyl]guanosine, also named as 2',3'-dideoxy-3'-fluoro-5-O-[2-(L-valyloxy)-propionyl]guanosine, is described in the WO 99/09031 and especially in example 32 therein.

30 Therefore, a preferred pharmaceutical composition useful for the treatment of viral infections comprises nevirapine and 3'-deoxy-3'-fluorothymidine or 3'-deoxy-3'-fluoro-5-O-[2-(L-

- 11 -

valyloxy)-propionyl]guanosine, or a pharmaceutically acceptable salt or prodrug thereof.

Furthermore, nevirapine in combination or alternation with
5 preferably 3'-deoxy-3'-fluorothymidine or 3'-deoxy-3'-fluoro-
5-O-[2-(L-valyloxy)-propionyl]guanosine, or a pharmaceutically acceptable salt or prodrug thereof, is used in the prophylaxis or treatment of a viral infection in a patient.

10 Also preferred is the use of nevirapine in combination with 3'-deoxy-3'-fluorothymidine or 3'-deoxy-3'-fluoro-5-O-[2-(L-valyloxy)-propionyl]guanosine, or a pharmaceutically acceptable salt or prodrug thereof, for the manufacture of a medicament for the prophylaxis or treatment of a viral
15 infection in a patient.

A preferred kit of parts for the prophylaxis or treatment of a viral infection in a patient, comprises

(a) a first containment containing a pharmaceutical
20 composition comprising nevirapine and a pharmaceutically acceptable carrier, and
(b) a second containment containing a pharmaceutical
composition comprising 3'-deoxy-3'-fluorothymidine or 3'-
deoxy-3'-fluoro-5-O-[2-(L-valyloxy)-propionyl]guanosine, or a
25 pharmaceutically acceptable salt or prodrug thereof, and a pharmaceutically acceptable carrier.

A preferred manufacture comprises nevirapine and 3'-deoxy-3'-fluorothymidine or 3'-deoxy-3'-fluoro-5-O-[2-(L-valyloxy)-propionyl]guanosine, or a pharmaceutically acceptable salt or prodrug thereof, for use in combination or alternation in the prophylaxis or treatment of a viral infection in a patient.

The advantageous effects of the combination of nevirapine and
35 the compound of formula (I) are realized over a wide ratio, like for example in a ratio of between 1:250 to 250:1.

- 12 -

Therefore, in the compositions, combinations, kit of parts, manufacture and/or the use of the combinations according to this invention, nevirapine and the at least one compound of formula (I), which is preferably 3'-deoxy-3'-fluorothymidine, 5 or a pharmaceutically acceptable salt or prodrug thereof, are preferably present in a synergistic ratio. Usually, this ratio is between about 1:250 to about 250:1. More preferably the ratio is between about 1:50 to about 50:1. The most preferred ratio is between about 1:20 to about 20:1, which includes the 10 ratios 1:18, 1:16, 1:14, 1:12, 1:10; 1:8; 1:6; 1:5; 1:4; 1:3; 1:2.5; 1:2; 1:1.5; 1:1.2; 1:1; 1,2:1; 1.5:1; 2:1; 2.5:1; 3:1; 4:1; 5:1; 6:1; 8:1; 10:1, 12:1, 14:1, 16:1, 18:1 and all ranges in between. If a further therapeutic agent is added, ratios will be adjusted accordingly.

15 It will be appreciated that the amount of pharmaceutical composition according to the invention required for use in treatment or prophylaxis will vary not only with the particular compound selected but also with the route of 20 administration, the nature and severity of the condition for which treatment or prophylaxis is required, the age, weight and condition of the patient, concomitant medication and will be ultimately at the discretion of the attendant physician or veterinarian. In general however the active compounds are 25 included in the pharmaceutically acceptable carrier in an amount sufficient to deliver to a patient a therapeutically effective amount of compound to inhibit viral replication in vivo, especially HIV replication, without causing serious toxic effects in the treated patient. By "inhibitory amount" 30 is meant an amount of active ingredient sufficient to exert an inhibitory effect as measured by, for example, an assay such as the ones described herein. A suitable dose will preferably be in the range of from about 0.05 to about 200 mg/kg of body weight per day.

35

The desired dose may conveniently be presented in a single dose or as divided dose administered at appropriate

intervals, for example as two, three, four or more doses per day.

5 The pharmaceutical composition according to the present invention is conveniently administered in unit dosage form; for example containing 5 to 3000 mg, conveniently 5 to 1000 mg of active ingredient(s) per unit dosage form.

10 The pharmaceutical acceptable carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof. Examples of pharmaceutically acceptable carriers are magnesium stearate, chalk, starch, lactose, wax, gum or gelatin. Carriers which are suited to achieve a sustained release, for 15 example natural or synthetic polymers or liposomes, are known to the one skilled in the art. Pharmaceutically acceptable carriers also comprise liquid carriers and diluents, for example water, alcohol, glycerine or oil, which serve as a base for liquid formulations, such as solutions, suspensions 20 or emulsions.

The compositions referred to above may conveniently be presented for use in the form of a pharmaceutical formulation and therefore pharmaceutical formulations 25 comprising a composition as defined above together with a pharmaceutically acceptable carrier comprise a further aspect of the invention.

30 The individual components of such compositions may be administered either in combination, i.e. simultaneously, or in alternation, i.e. sequentially, in separate or combined pharmaceutical formulations.

35 When nevirapine is used in combination with a compound of the formula (I) against the same virus the dose of each compound may be either the same as or differ from that when the

compound is used alone. Appropriate doses will be readily appreciated by those skilled in the art.

5 The compositions according to this invention preferably also comprise at least one pharmaceutically acceptable carrier.

According to the third aspect of this invention, the combination of nevirapine and at least one compound of the formula (I) is used for the manufacture of a medicament for
10 the prophylaxis or the treatment of a viral infection in a patient.

According to one embodiment, this medicament may be a unit dosage form, which is preferably useful in combination
15 therapy, such as capsules or tablets. The unit dosage form contains a pharmaceutical composition according to this invention, i.e. nevirapine in combination with at least one compound of the formula (I), with at least one pharmaceutically acceptable carrier.

20 Therefore, another object of this invention also comprises bringing nevirapine and at least a compound of the formula (I) together in conjunction or association with a pharmaceutically acceptable carrier.

25 According to another embodiment, this medicament is a multiple dosage form, preferably a kit of parts, which is especially useful in alternation and/or combination therapy to flexibly suit the individual therapeutic needs of the patient.

According to further embodiments the combinations, compositions, kit of parts, manufactures of this invention and the uses thereof comprise a combination selected from the group consisting of:

- 5 ■ a compound of the formula (I), nevirapine and one, two or more further NRTIs;
- a compound of the formula (I), nevirapine, a protease inhibitor and optionally one, two or more further NRTIs;
- a compound of the formula (I), nevirapine, an entry inhibitor and optionally one, two or more further NRTIs;
- 10 ■ a compound of the formula (I), nevirapine, a protease inhibitor, an entry inhibitor and optionally one, two or more further NRTIs;
- a compound of the formula (I), nevirapine, a protease inhibitor, an integrase inhibitor and optionally one, two or more further NRTIs.
- 15 ■ a compound of the formula (I), nevirapine, a protease inhibitor, an integrase inhibitor and optionally one, two or more further NRTIs.

In the above listed combinations, compositions, kit of parts, manufactures and uses thereof a protease inhibitor may advantageously be combined with ritonavir in order to improve 20 the pharmacokinetics of said protease inhibitor.

In the foregoing and in the following, the term "further NRTI" refers to a nucleoside reverse transcriptase inhibitor, or a 25 pharmaceutically acceptable salt or prodrug thereof, other than the selected compound of the formula (I). Examples of further NRTIs are Abacavir Sulfate (Ziagen), Didanosine (ddI, Videx), Emtricitabine (Emtriva), Lamivudine (3TC, Epivir), Stavudine (d4t, Zerit), Tenofovir disoproxil fumarate 30 (nucleotide, bis (POC) PMPA, Viread), Zalcitabine (ddc, Hivid), Zidovudine (AZT, Retrovir), Amdoxovir (DAPD; Gilead Sciences), Elvucitabine (ACH-126443; Achillion Pharm.), GS-7340 (Gilead Sciences), INK-20 (thioether phospholipid formulation of AZT; Kucera Pharm.), MIV-310 (Medivir AB), MIV-35 210 (Medivir AB), Racivir (racemic FTC; Pharmasset), Reverset (RVT, D-D4FC, DPC-817; Pharmasset), SPD-754 ((-)dOTC; Shire Pharm), BCH-13520 (Shire Pharm) and BCH-10618 (Shire Pharm).

- 16 -

In the foregoing and in the following, the term "protease inhibitor" refers to a protease inhibitor, or a pharmaceutically acceptable salt or prodrug thereof. Examples 5 of protease inhibitors are Amprenavir (VX-478, Agenerase), Atazanavir (Reyataz), Indinavir Sulfate (MK-639, Crixivan), Lexiva (fosamprenavir calcium, GW -433908 or 908, VX-175), Lopinavir + Ritonavir (ABT-378/r, Kaletra), Nelfinavir Mesylate (Viracept), Ritonavir (ABT-538, Norvir), Saquinavir 10 (Invirase, Fortovase), Tipranavir + Ritonavir, AG-1776 (JE-2147, KNI-764; Nippon Mining Holdings), AG-1859 (Pfizer), DPC-681/684 (BMS), GS224338 ('4338; Gilead Sciences), KNI-272 (Nippon Mining Holdings), Nar-DG-35 (Narhex), P(PL)-100 (P-1946; Procyon Biopharma), P-1946 (Procyon Biopharma), R-944 15 (Hoffmann-LaRoche), RO-0334649 (Hoffmann-LaRoche), TMC-114 (Johnson & Johnson), VX-385 (GW-640385; GSK/Vertex) and VX-478 (Vertex/GSK).

In the foregoing and in the following, the term "entry inhibitor" refers to an entry inhibitor, including fusion 20 inhibitors, inhibitors of the CD4 receptor, inhibitors of the CCR5 co-receptor and inhibitors of the CXCR4 co-receptor, or a pharmaceutically acceptable salt or prodrug thereof. Examples of entry inhibitors are AMD-070 (AMD-11070; AnorMed), 25 BlockAide/CR (ADVENTRX Pharm.), BMS 806 (BMS-378806; BMS), Enfurvirtide (T-20, R698, Fuzeon), KRH-1636 (Kureha Pharmaceuticals), ONO-4128 (GW-873140, AK-602, E-913; ONO Pharmaceuticals), Pro-140 (Progenics Pharm), PRO-542 (Progenics Pharm.), SCH-D (SCH-417690; Schering-Plough), T-30 1249 (R724; Roche/Trimeris), TAK-220 (Takeda Chem. Ind.), TNX-355 (Tanox) and UK-427,857 (Pfizer).

Examples of an integrase inhibitors are L-870810 (Merck & Co.), c-2507 (Merck & Co.) and S(RSC)-1838 (Shionogi/GSK).

35

According to still further embodiments the combinations, compositions, kit of parts, manufactures of this invention and

the uses thereof comprise a combination selected from the group consisting of a compound of the formula (I), nevirapine and a further antiviral agent.

5 A further antiviral agent may be selected from the group of the maturation inhibitors, antisense compounds or NNRTIs, other than nevirapine. Examples of further antivirals are PA-457 (Panacos), KPC-2 (Kucera Pharm.), HGTB-43 (Enzo Biochem), Delavirdine (Rescriptor), Efavirenz (DMP-266, Sustiva), (+)-
10 Calanolide A and B (Advanced Life Sciences), Capravirine (AG1549, S-1153; Pfizer), GW-695634 (GW-8248; GSK), MIV-150 (Medivir), MV026048 (R-1495; Medivir AB/Roche), NV-05 (Idenix Pharm.), R-278474 (Johnson & Johnson), RS-1588 (Idenix Pharm.), TMC-120/125 (Johnson & Johnson), TMC-125 (R-165335;
15 Johnson & Johnson), UC-781 (Biosyn Inc.) and YM-215389 (Yamanoushi).

The combinations, compositions, kit of parts, manufactures of this invention and the uses thereof of the above mentioned
20 embodiments may be combined with further active ingredients.

Examples of such further active ingredients are acyclic nucleosides such as acyclovir, ganciclovir; interferons such as alpha-, beta- and gamma-interferon; glucuronation
25 inhibitors such as probenecid; nucleoside transport inhibitors such as dipyridamole; immunomodulators such as interleukin II (IL2) and granulocyte macrophage colony stimulating factor (GM-CSF), erythropoietin, ampligen, thymomodulin, thymopentin, foscarnet, glycosylation inhibitors such as 2-deoxy-D-glucose,
30 castanospermine, 1-deoxynojirimycin; and inhibitors of HIV binding to CD4 receptors such as soluble CD4, CD4 fragments, CD4-hybrid molecules and inhibitors of the HIV aspartyl protease such as L-735,524.

35 The compounds, or their pharmaceutically acceptable derivative or salts thereof, can also be mixed with other active materials that do not impair the desired action, or with

materials that supplement the desired action, such as antibiotics, antifungals, antiinflammatories, protease inhibitors, or other nucleoside or non-nucleoside antiviral agents, as discussed in more detail above.

5

In general, during alternation therapy, an effective dosage of each agent is administered serially, whereas in combination therapy, an effective dosage of two or more agents are administered together. The dosages will depend on such factors 10 as absorption, biodistribution, metabolism and excretion rates for each drug as well as other factors known to those of skill in the art. It is to be noted that dosage values will also vary with the severity of the condition to be alleviated. It is to be further understood that for any particular subject, 15 specific dosage regimens and schedules should be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the compositions. Examples of suitable dosage ranges for nevirapine, compounds of formula (I), 20 preferably 3'-deoxy-3'-fluorothymidine, further NRTIs and other antivirals can be found in the scientific literature. Many examples of suitable dosage ranges for other compounds described herein are also found in the public literature or 25 can be identified using known procedures. These dosage ranges can be modified as desired to achieve a desired result.

It has been recognized that drug-resistant variants of HIV can emerge after prolonged treatment with an antiviral agent. Drug resistance most typically occurs by mutation of a gene that 30 encodes for an enzyme used in the viral life cycle, and most typically in the case of HIV, in either the reverse transcriptase or protease genes. It has been demonstrated that the efficacy of a drug against HIV infection can be prolonged, augmented, or restored by administering the compound in 35 combination or alternation with a second, and perhaps third, antiviral compound that induces a different mutation(s) from that selected for by the principle drug. Alternatively, the

pharmacokinetics, biodistribution, or other parameter of the drug can be altered by such combination or alternation therapy. In general, combination therapy is typically preferred over alternation therapy because it induces multiple 5 simultaneous stresses on the virus. In the case of administering the antiviral coomponents in alternation, i.e. sequentially, the time gap between administering the first compound and the second compound is preferably not too long in order to achieve a beneficial effect. Preferably, the time gap 10 is less than half a day, most preferably less than 6 hours.

While it is possible that, for use in therapy, a compound of the invention may be administered as the raw chemical it is preferable to present the active ingredient as a 15 pharmaceutical formulation. The invention thus further provides a pharmaceutical formulation comprising nevirapine and a compound of the formula (I) with one or more pharmaceutically acceptable carriers and, optionally, other therapeutic and/or prophylactic ingredients.

20 Pharmaceutical formulations include those suitable for oral, rectal, nasal, topical (including buccal and sub lingual), transdermal, vaginal or parenteral (including intramuscular, sub-cutaneous and intravenous) administration 25 in liquid or solid form or in a form suitable for administration by inhalation or insufflation. The formulations may, where appropriate, be conveniently presented in discrete dosage units and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of 30 bringing into association the active compound(s) with liquid carriers or finely divided solid carriers or both and then, if necessary, shaping the product into the desired formulation.

35 Pharmaceutical formulation suitable for oral administration may conveniently be presented as discrete units such as capsules, including soft gelatin capsules, cachets or tablets

each containing a predetermined amount of the active ingredient(s); as a powder or granules; as a solution, a suspension or as an emulsion, for example as syrups, elixirs or self-emulsifying delivery systems (SEDDS). The active 5 ingredient(s) may also be presented as a bolus, electuary or paste. Tablets and capsules for oral administration may contain conventional excipients such as binding agents, fillers, lubricants, disintegrants, or wetting agents. The tablets may be coated according to methods well known in the 10 art. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, or may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives 15 such as suspending agents, emulsifying agents, non-aqueous vehicles (which may include edible oils), or preservatives.

The pharmaceutical composition according to the invention may also be formulated for parenteral administration (e.g. 20 by injection, for example bolus injection or continuous infusion) and may be presented in unit dose form in ampoules, pre-filled syringes, small volume infusion or in multi-dose containers with an added preservative. The compositions may take such forms as suspensions, 25 solutions, or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents. Alternatively, the active ingredient(s) may be in powder form, obtained by aseptic isolation of sterile solid or by lyophilisation 30 from solution, for constitution with a suitable vehicle, e.g. sterile, pyrogen-free water, before use.

Pharmaceutical formulations suitable for rectal administration wherein the carrier is a solid are most 35 preferably presented as unit dose suppositories. Suitable carriers include cocoa butter and other materials commonly used in the art, and the suppositories may be conveniently

formed by admixture of the active compound(s) with the softened or melted carrier(s) followed by chilling and shaping in moulds.

5 When desired the above described formulations adapted to give sustained release of the active ingredient(s) may be employed.

The compositions, combinations, kit of parts, manufacture and/or the use of the combinations according to this invention 10 are advantageous in the treatment and/or prophylaxis of viral infections in a patient, preferably human retrovirus (HRV) infections and hepatitis B, in particular HIV infections, especially multiresistant HIV infections. Therefore this 15 invention may offer an aid especially for highly treatment experienced patients suffering from multiresistant HIV. In addition to the treatment of said diseases, the combinations, formulations and compositions according to this invention can be used prophylactically to prevent or retard the progression 20 of clinical illness in individuals who are anti-HIV antibody or HIV-antigen positive or who have been exposed to HIV.

The compositions, combinations, kit of parts, manufacture and/or the use of the combinations according to this invention 25 may also be beneficial in preventing perinatal transmission of human retroviral (HRV) infections, in particular HIV-1, from mother to baby. According to this method, nevirapine and a compound of the formula (I), preferably 3'-deoxy-3'-fluorothymidine, and optionally further active compounds as 30 described hereinbefore or hereinafter are administered in combination or alternation to the mother before giving birth.

The compositions, combinations, kit of parts, manufacture and/or the use of the combinations according to this invention 35 may also be beneficial in the treatment and/or prophylaxis of other HIV/AIDS-related conditions such as AIDS-related complex (ARC), persistent generalized lymphadenopathy (PGL), AIDS-

related neurological conditions, anti-HIV antibody positive and HIV-positive conditions, Kaposi's sarcoma, thrombocytopenia purpurea and opportunistic infections.

5 Therefore, patients to be treated would be especially those individuals:

1) infected with one or more strains of a human retrovirus as determined by the presence of either measurable viral antibody or antigen in the serum; and/or

10 2) in the case of HIV, having either a asymptomatic HIV infection or a symptomatic AIDS defining infection such as i) disseminated histoplasmosis, ii) isopsoriasis, iii) bronchial and pulmonary candidiasis including pneumocystic pneumonia, iv) non-Hodgkin's lymphoma or v) Kaposi's sarcoma and being
15 less than sixty years old; or having an absolute CD4+ lymphocyte count of less than 500/mm³ in the peripheral blood.

The pharmaceutical combination according to this invention can be tested for additive and synergistic activity against HIV
20 according to a number of assays known in scientific and public literature, including the one described in the WO 98/44913 and WO 00/51641, which are included herein by way of reference.

The present invention is illustrated in further detail by the
25 following non-limiting examples of combinations according to this invention, comprising a 1st compound, a 2nd compound, optionally a 3rd compound, optionally a 4th compound and optionally a 5th compound.

30 Table 1 illustrating combinations of a compound of the formula (I), nevirapine and one, two or more further NRTIs

| 1 st compound | 2 nd compound | 3 rd compound |
|--------------------------|--------------------------|--------------------------|
| FLT | Nevirapine | Abacavir Sulfate |

| | | |
|-----|------------|-------------------------------------|
| FLT | Nevirapine | Didanosine |
| FLT | Nevirapine | Emtricitabine |
| FLT | Nevirapine | Lamivudine |
| FLT | Nevirapine | Stavudine |
| FLT | Nevirapine | Tenofovir disoproxil fumarate |
| FLT | Nevirapine | Zalcitabine |
| FLT | Nevirapine | Zidovudine |
| FLT | Nevirapine | Amdoxovir |
| FLT | Nevirapine | Elvucitabine |
| FLT | Nevirapine | GS-7340 |
| FLT | Nevirapine | INK-20 |
| FLT | Nevirapine | MIV-210 |
| FLT | Nevirapine | Racivir |
| FLT | Nevirapine | Reverset |
| FLT | Nevirapine | SPD-754 |
| FLT | Nevirapine | BCH-13520 |
| FLT | Nevirapine | BCH-10618 |
| FLG | Nevirapine | Abacavir Sulfate |
| FLG | Nevirapine | Didanosine |
| FLG | Nevirapine | Emtricitabine |
| FLG | Nevirapine | Lamivudine |
| FLG | Nevirapine | Stavudine |
| FLG | Nevirapine | Tenofovir disoproxil fumarate |
| FLG | Nevirapine | Zalcitabine |

- 24 -

| | | |
|-----|------------|--------------|
| FLG | Nevirapine | Zidovudine |
| FLG | Nevirapine | Amdoxovir |
| FLG | Nevirapine | Elvucitabine |
| FLG | Nevirapine | GS-7340 |
| FLG | Nevirapine | INK-20 |
| FLG | Nevirapine | MIV-310 |
| FLG | Nevirapine | Racivir |
| FLG | Nevirapine | Reverset |
| FLG | Nevirapine | SPD-754 |
| FLG | Nevirapine | BCH-13520 |
| FLG | Nevirapine | BCH-10618 |

Table 2 illustrating combinations of a compound of the formula (I), nevirapine, a protease inhibitor and optionally one, two or more further NRTIs

5

| 1 st compound | 2 nd compound | 3 rd compound |
|--------------------------|--------------------------|---------------------------|
| FLT | Nevirapine | Amprenavir |
| FLT | Nevirapine | Atazanavir |
| FLT | Nevirapine | Indinavir Sulfate |
| FLT | Nevirapine | Lexiva |
| FLT | Nevirapine | Lopinavir + Ritonavir |
| FLT | Nevirapine | Nelfinavir Mesylate |
| FLT | Nevirapine | Ritonavir |
| FLT | Nevirapine | Saquinavir |
| FLT | Nevirapine | Tipranavir + Ritonavir |

| | | |
|-----|------------|---------------------------|
| FLT | Nevirapine | AG-1776 |
| FLT | Nevirapine | AG-1859 |
| FLT | Nevirapine | DPC-681/684 |
| FLT | Nevirapine | GS224338 |
| FLT | Nevirapine | KNI-272 |
| FLT | Nevirapine | Nar-DG-35 |
| FLT | Nevirapine | P(PL)-100 |
| FLT | Nevirapine | P-1946 |
| FLT | Nevirapine | R-944 |
| FLT | Nevirapine | RO-0334649 |
| FLT | Nevirapine | TMC-114 |
| FLT | Nevirapine | VX-385 |
| FLT | Nevirapine | VX-478 |
| FLG | Nevirapine | Amprenavir |
| FLG | Nevirapine | Atazanavir |
| FLG | Nevirapine | Indinavir Sulfate |
| FLG | Nevirapine | Lexiva |
| FLG | Nevirapine | Lopinavir + Ritonavir |
| FLG | Nevirapine | Nelfinavir Mesylate |
| FLG | Nevirapine | Ritonavir |
| FLG | Nevirapine | Saquinavir |
| FLG | Nevirapine | Tipranavir + Ritonavir |
| FLG | Nevirapine | AG-1776 |
| FLG | Nevirapine | AG-1859 |

| | | |
|-----|------------|-------------|
| FLG | Nevirapine | DPC-681/684 |
| FLG | Nevirapine | GS224338 |
| FLG | Nevirapine | KNI-272 |
| FLG | Nevirapine | Nar-DG-35 |
| FLG | Nevirapine | P(PL)-100 |
| FLG | Nevirapine | P-1946 |
| FLG | Nevirapine | R-944 |
| FLG | Nevirapine | RO-0334649 |
| FLG | Nevirapine | TMC-114 |
| FLG | Nevirapine | VX-385 |
| FLG | Nevirapine | VX-478 |

Table 3 illustrating combinations of a compound of the formula (I), nevirapine, an entry inhibitor and optionally one, two or more further NRTIs

5

| 1 st compound | 2 nd compound | 3 rd compound |
|--------------------------|--------------------------|--------------------------|
| FLT | Nevirapine | Enfurvirtide |
| FLT | Nevirapine | T-1249 |
| FLT | Nevirapine | AMD-070 |
| FLT | Nevirapine | BlockAide/CR |
| FLT | Nevirapine | BMS 806 |
| FLT | Nevirapine | KRH-1636 |
| FLT | Nevirapine | ONO-4128 |
| FLT | Nevirapine | Pro-140 |
| FLT | Nevirapine | PRO-542 |
| FLT | Nevirapine | SCH-D |
| FLT | Nevirapine | TAK-220 |
| FLT | Nevirapine | TNX-355 |

- 27 -

| | | |
|-----|------------|--------------|
| FLT | Nevirapine | UK-427,857 |
| FLG | Nevirapine | Enfurvirtide |
| FLG | Nevirapine | T-1249 |
| FLG | Nevirapine | AMD-070 |
| FLG | Nevirapine | BlockAide/CR |
| FLG | Nevirapine | BMS 806 |
| FLG | Nevirapine | KRH-1636 |
| FLG | Nevirapine | ONO-4128 |
| FLG | Nevirapine | Pro-140 |
| FLG | Nevirapine | PRO-542 |
| FLG | Nevirapine | SCH-D |
| FLG | Nevirapine | TAK-220 |
| FLG | Nevirapine | TNX-355 |
| FLG | Nevirapine | UK-427,857 |

Table 4 illustrating combinations of a compound of the formula (I), nevirapine, a protease inhibitor, an entry inhibitor and optionally one, two or more further NRTIs

5

| 1 st compound | 2 nd compound | 3 rd compound | 4 th compound |
|-----------------------------|-----------------------------|--------------------------|--------------------------|
| FLT | Nevirapine | Amprenavir | Enfurvirtide |
| FLT | Nevirapine | Amprenavir | T-1249 |
| FLT | Nevirapine | Amprenavir | AMD-070 |
| FLT | Nevirapine | Amprenavir | BlockAide/CR |
| FLT | Nevirapine | Amprenavir | BMS 806 |
| FLT | Nevirapine | Amprenavir | KRH-1636 |
| FLT | Nevirapine | Amprenavir | ONO-4128 |
| FLT | Nevirapine | Amprenavir | Pro-140 |

| | | | |
|-----|------------|----------------------|--------------|
| FLT | Nevirapine | Amprenavir | PRO-542 |
| FLT | Nevirapine | Amprenavir | SCH-D |
| FLT | Nevirapine | Amprenavir | TAK-220 |
| FLT | Nevirapine | Amprenavir | TNX-355 |
| FLT | Nevirapine | Amprenavir | UK-427,857 |
| FLT | Nevirapine | Atazanavir | Enfurvirtide |
| FLT | Nevirapine | Atazanavir | T-1249 |
| FLT | Nevirapine | Atazanavir | AMD-070 |
| FLT | Nevirapine | Atazanavir | BlockAide/CR |
| FLT | Nevirapine | Atazanavir | BMS 806 |
| FLT | Nevirapine | Atazanavir | KRH-1636 |
| FLT | Nevirapine | Atazanavir | ONO-4128 |
| FLT | Nevirapine | Atazanavir | Pro-140 |
| FLT | Nevirapine | Atazanavir | PRO-542 |
| FLT | Nevirapine | Atazanavir | SCH-D |
| FLT | Nevirapine | Atazanavir | TAK-220 |
| FLT | Nevirapine | Atazanavir | TNX-355 |
| FLT | Nevirapine | Atazanavir | UK-427,857 |
| FLT | Nevirapine | Indinavir Sulfate | Enfurvirtide |
| FLT | Nevirapine | Indinavir Sulfate | T-1249 |
| FLT | Nevirapine | Indinavir Sulfate | AMD-070 |
| FLT | Nevirapine | Indinavir Sulfate | BlockAide/CR |
| FLT | Nevirapine | Indinavir Sulfate | BMS 806 |

| | | | |
|-----|------------|-------------------|--------------|
| FLT | Nevirapine | Indinavir Sulfate | KRH-1636 |
| FLT | Nevirapine | Indinavir Sulfate | ONO-4128 |
| FLT | Nevirapine | Indinavir Sulfate | Pro-140 |
| FLT | Nevirapine | Indinavir Sulfate | PRO-542 |
| FLT | Nevirapine | Indinavir Sulfate | SCH-D |
| FLT | Nevirapine | Indinavir Sulfate | TAK-220 |
| FLT | Nevirapine | Indinavir Sulfate | TNX-355 |
| FLT | Nevirapine | Indinavir Sulfate | UK-427,857 |
| FLT | Nevirapine | Lexiva | Enfurvirtide |
| FLT | Nevirapine | Lexiva | T-1249 |
| FLT | Nevirapine | Lexiva | AMD-070 |
| FLT | Nevirapine | Lexiva | BlockAide/CR |
| FLT | Nevirapine | Lexiva | BMS 806 |
| FLT | Nevirapine | Lexiva | KRH-1636 |
| FLT | Nevirapine | Lexiva | ONO-4128 |
| FLT | Nevirapine | Lexiva | Pro-140 |
| FLT | Nevirapine | Lexiva | PRO-542 |
| FLT | Nevirapine | Lexiva | SCH-D |
| FLT | Nevirapine | Lexiva | TAK-220 |
| FLT | Nevirapine | Lexiva | TNX-355 |
| FLT | Nevirapine | Lexiva | UK-427,857 |

- 30 -

| | | | |
|-----|------------|-----------------------|--------------|
| FLT | Nevirapine | Lopinavir + Ritonavir | Enfurvirtide |
| FLT | Nevirapine | Lopinavir + Ritonavir | T-1249 |
| FLT | Nevirapine | Lopinavir + Ritonavir | AMD-070 |
| FLT | Nevirapine | Lopinavir + Ritonavir | BlockAide/CR |
| FLT | Nevirapine | Lopinavir + Ritonavir | BMS 806 |
| FLT | Nevirapine | Lopinavir + Ritonavir | KRH-1636 |
| FLT | Nevirapine | Lopinavir + Ritonavir | ONO-4128 |
| FLT | Nevirapine | Lopinavir + Ritonavir | Pro-140 |
| FLT | Nevirapine | Lopinavir + Ritonavir | PRO-542 |
| FLT | Nevirapine | Lopinavir + Ritonavir | SCH-D |
| FLT | Nevirapine | Lopinavir + Ritonavir | TAK-220 |
| FLT | Nevirapine | Lopinavir + Ritonavir | TNX-355 |
| FLT | Nevirapine | Lopinavir + Ritonavir | UK-427,857 |
| FLT | Nevirapine | Nelfinavir Mesylate | Enfurvirtide |
| FLT | Nevirapine | Nelfinavir Mesylate | T-1249 |
| FLT | Nevirapine | Nelfinavir | AMD-070 |

| | | Mesylate | |
|-----|------------|---------------------|--------------|
| FLT | Nevirapine | Nelfinavir Mesylate | BlockAide/CR |
| FLT | Nevirapine | Nelfinavir Mesylate | BMS 806 |
| FLT | Nevirapine | Nelfinavir Mesylate | KRH-1636 |
| FLT | Nevirapine | Nelfinavir Mesylate | ONO-4128 |
| FLT | Nevirapine | Nelfinavir Mesylate | Pro-140 |
| FLT | Nevirapine | Nelfinavir Mesylate | PRO-542 |
| FLT | Nevirapine | Nelfinavir Mesylate | SCH-D |
| FLT | Nevirapine | Nelfinavir Mesylate | TAK-220 |
| FLT | Nevirapine | Nelfinavir Mesylate | TNX-355 |
| FLT | Nevirapine | Nelfinavir Mesylate | UK-427,857 |
| FLT | Nevirapine | Ritonavir | Enfurvirtide |
| FLT | Nevirapine | Ritonavir | T-1249 |
| FLT | Nevirapine | Ritonavir | AMD-070 |
| FLT | Nevirapine | Ritonavir | BlockAide/CR |
| FLT | Nevirapine | Ritonavir | BMS 806 |
| FLT | Nevirapine | Ritonavir | KRH-1636 |
| FLT | Nevirapine | Ritonavir | ONO-4128 |
| FLT | Nevirapine | Ritonavir | Pro-140 |
| FLT | Nevirapine | Ritonavir | PRO-542 |

| | | | |
|-----|------------|---------------------------|--------------|
| FLT | Nevirapine | Ritonavir | SCH-D |
| FLT | Nevirapine | Ritonavir | TAK-220 |
| FLT | Nevirapine | Ritonavir | TNX-355 |
| FLT | Nevirapine | Ritonavir | UK-427,857 |
| FLT | Nevirapine | Saquinavir | Enfurvirtide |
| FLT | Nevirapine | Saquinavir | T-1249 |
| FLT | Nevirapine | Saquinavir | AMD-070 |
| FLT | Nevirapine | Saquinavir | BlockAide/CR |
| FLT | Nevirapine | Saquinavir | BMS 806 |
| FLT | Nevirapine | Saquinavir | KRH-1636 |
| FLT | Nevirapine | Saquinavir | ONO-4128 |
| FLT | Nevirapine | Saquinavir | Pro-140 |
| FLT | Nevirapine | Saquinavir | PRO-542 |
| FLT | Nevirapine | Saquinavir | SCH-D |
| FLT | Nevirapine | Saquinavir | TAK-220 |
| FLT | Nevirapine | Saquinavir | TNX-355 |
| FLT | Nevirapine | Saquinavir | UK-427,857 |
| FLT | Nevirapine | Tipranavir + Ritonavir | Enfurvirtide |
| FLT | Nevirapine | Tipranavir + Ritonavir | T-1249 |
| FLT | Nevirapine | Tipranavir + Ritonavir | AMD-070 |
| FLT | Nevirapine | Tipranavir + Ritonavir | BlockAide/CR |
| FLT | Nevirapine | Tipranavir + Ritonavir | BMS 806 |
| FLT | Nevirapine | Tipranavir + Ritonavir | KRH-1636 |

- 33 -

| | | | |
|-----|------------|---------------------------|--------------|
| FLT | Nevirapine | Tipranavir + Ritonavir | ONO-4128 |
| FLT | Nevirapine | Tipranavir + Ritonavir | Pro-140 |
| FLT | Nevirapine | Tipranavir + Ritonavir | PRO-542 |
| FLT | Nevirapine | Tipranavir + Ritonavir | SCH-D |
| FLT | Nevirapine | Tipranavir + Ritonavir | TAK-220 |
| FLT | Nevirapine | Tipranavir + Ritonavir | TNX-355 |
| FLT | Nevirapine | Tipranavir + Ritonavir | UK-427,857 |
| FLG | Nevirapine | Amprenavir | Enfurvirtide |
| FLG | Nevirapine | Amprenavir | T-1249 |
| FLG | Nevirapine | Amprenavir | AMD-070 |
| FLG | Nevirapine | Amprenavir | BlockAide/CR |
| FLG | Nevirapine | Amprenavir | BMS 806 |
| FLG | Nevirapine | Amprenavir | KRH-1636 |
| FLG | Nevirapine | Amprenavir | ONO-4128 |
| FLG | Nevirapine | Amprenavir | Pro-140 |
| FLG | Nevirapine | Amprenavir | PRO-542 |
| FLG | Nevirapine | Amprenavir | SCH-D |
| FLG | Nevirapine | Amprenavir | TAK-220 |
| FLG | Nevirapine | Amprenavir | TNX-355 |
| FLG | Nevirapine | Amprenavir | UK-427,857 |
| FLG | Nevirapine | Atazanavir | Enfurvirtide |
| FLG | Nevirapine | Atazanavir | T-1249 |

| | | | |
|-----|------------|----------------------|--------------|
| FLG | Nevirapine | Atazanavir | AMD-070 |
| FLG | Nevirapine | Atazanavir | BlockAide/CR |
| FLG | Nevirapine | Atazanavir | BMS 806 |
| FLG | Nevirapine | Atazanavir | KRH-1636 |
| FLG | Nevirapine | Atazanavir | ONO-4128 |
| FLG | Nevirapine | Atazanavir | Pro-140 |
| FLG | Nevirapine | Atazanavir | PRO-542 |
| FLG | Nevirapine | Atazanavir | SCH-D |
| FLG | Nevirapine | Atazanavir | TAK-220 |
| FLG | Nevirapine | Atazanavir | TNX-355 |
| FLG | Nevirapine | Atazanavir | UK-427,857 |
| FLG | Nevirapine | Indinavir Sulfate | Enfurvirtide |
| FLG | Nevirapine | Indinavir Sulfate | T-1249 |
| FLG | Nevirapine | Indinavir Sulfate | AMD-070 |
| FLG | Nevirapine | Indinavir Sulfate | BlockAide/CR |
| FLG | Nevirapine | Indinavir Sulfate | BMS 806 |
| FLG | Nevirapine | Indinavir Sulfate | KRH-1636 |
| FLG | Nevirapine | Indinavir Sulfate | ONO-4128 |
| FLG | Nevirapine | Indinavir Sulfate | Pro-140 |
| FLG | Nevirapine | Indinavir Sulfate | PRO-542 |

| | | | |
|-----|------------|-----------------------|--------------|
| FLG | Nevirapine | Indinavir Sulfate | SCH-D |
| FLG | Nevirapine | Indinavir Sulfate | TAK-220 |
| FLG | Nevirapine | Indinavir Sulfate | TNX-355 |
| FLG | Nevirapine | Indinavir Sulfate | UK-427,857 |
| FLG | Nevirapine | Lexiva | Enfurvirtide |
| FLG | Nevirapine | Lexiva | T-1249 |
| FLG | Nevirapine | Lexiva | AMD-070 |
| FLG | Nevirapine | Lexiva | BlockAide/CR |
| FLG | Nevirapine | Lexiva | BMS 806 |
| FLG | Nevirapine | Lexiva | KRH-1636 |
| FLG | Nevirapine | Lexiva | ONO-4128 |
| FLG | Nevirapine | Lexiva | Pro-140 |
| FLG | Nevirapine | Lexiva | PRO-542 |
| FLG | Nevirapine | Lexiva | SCH-D |
| FLG | Nevirapine | Lexiva | TAK-220 |
| FLG | Nevirapine | Lexiva | TNX-355 |
| FLG | Nevirapine | Lexiva | UK-427,857 |
| FLG | Nevirapine | Lopinavir + Ritonavir | Enfurvirtide |
| FLG | Nevirapine | Lopinavir + Ritonavir | T-1249 |
| FLG | Nevirapine | Lopinavir + Ritonavir | AMD-070 |
| FLG | Nevirapine | Lopinavir + Ritonavir | BlockAide/CR |

| | | | |
|-----|------------|-----------------------|--------------|
| FLG | Nevirapine | Lopinavir + Ritonavir | BMS 806 |
| FLG | Nevirapine | Lopinavir + Ritonavir | KRH-1636 |
| FLG | Nevirapine | Lopinavir + Ritonavir | ONO-4128 |
| FLG | Nevirapine | Lopinavir + Ritonavir | Pro-140 |
| FLG | Nevirapine | Lopinavir + Ritonavir | PRO-542 |
| FLG | Nevirapine | Lopinavir + Ritonavir | SCH-D |
| FLG | Nevirapine | Lopinavir + Ritonavir | TAK-220 |
| FLG | Nevirapine | Lopinavir + Ritonavir | TNX-355 |
| FLG | Nevirapine | Lopinavir + Ritonavir | UK-427,857 |
| FLG | Nevirapine | Nelfinavir Mesylate | Enfurvirtide |
| FLG | Nevirapine | Nelfinavir Mesylate | T-1249 |
| FLG | Nevirapine | Nelfinavir Mesylate | AMD-070 |
| FLG | Nevirapine | Nelfinavir Mesylate | BlockAide/CR |
| FLG | Nevirapine | Nelfinavir Mesylate | BMS 806 |
| FLG | Nevirapine | Nelfinavir Mesylate | KRH-1636 |
| FLG | Nevirapine | Nelfinavir Mesylate | ONO-4128 |

| | | Mesylate | |
|-----|------------|---------------------|--------------|
| FLG | Nevirapine | Nelfinavir Mesylate | Pro-140 |
| FLG | Nevirapine | Nelfinavir Mesylate | PRO-542 |
| FLG | Nevirapine | Nelfinavir Mesylate | SCH-D |
| FLG | Nevirapine | Nelfinavir Mesylate | TAK-220 |
| FLG | Nevirapine | Nelfinavir Mesylate | TNX-355 |
| FLG | Nevirapine | Nelfinavir Mesylate | UK-427,857 |
| FLG | Nevirapine | Ritonavir | Enfurvirtide |
| FLG | Nevirapine | Ritonavir | T-1249 |
| FLG | Nevirapine | Ritonavir | AMD-070 |
| FLG | Nevirapine | Ritonavir | BlockAide/CR |
| FLG | Nevirapine | Ritonavir | BMS 806 |
| FLG | Nevirapine | Ritonavir | KRH-1636 |
| FLG | Nevirapine | Ritonavir | ONO-4128 |
| FLG | Nevirapine | Ritonavir | Pro-140 |
| FLG | Nevirapine | Ritonavir | PRO-542 |
| FLG | Nevirapine | Ritonavir | SCH-D |
| FLG | Nevirapine | Ritonavir | TAK-220 |
| FLG | Nevirapine | Ritonavir | TNX-355 |
| FLG | Nevirapine | Ritonavir | UK-427,857 |
| FLG | Nevirapine | Saquinavir | Enfurvirtide |
| FLG | Nevirapine | Saquinavir | T-1249 |
| FLG | Nevirapine | Saquinavir | AMD-070 |

| | | | |
|-----|------------|---------------------------|--------------|
| FLG | Nevirapine | Saquinavir | BlockAide/CR |
| FLG | Nevirapine | Saquinavir | BMS 806 |
| FLG | Nevirapine | Saquinavir | KRH-1636 |
| FLG | Nevirapine | Saquinavir | ONO-4128 |
| FLG | Nevirapine | Saquinavir | Pro-140 |
| FLG | Nevirapine | Saquinavir | PRO-542 |
| FLG | Nevirapine | Saquinavir | SCH-D |
| FLG | Nevirapine | Saquinavir | TAK-220 |
| FLG | Nevirapine | Saquinavir | TNX-355 |
| FLG | Nevirapine | Saquinavir | UK-427,857 |
| FLG | Nevirapine | Tipranavir + Ritonavir | Enfurvirtide |
| FLG | Nevirapine | Tipranavir + Ritonavir | T-1249 |
| FLG | Nevirapine | Tipranavir + Ritonavir | AMD-070 |
| FLG | Nevirapine | Tipranavir + Ritonavir | BlockAide/CR |
| FLG | Nevirapine | Tipranavir + Ritonavir | BMS 806 |
| FLG | Nevirapine | Tipranavir + Ritonavir | KRH-1636 |
| FLG | Nevirapine | Tipranavir + Ritonavir | ONO-4128 |
| FLG | Nevirapine | Tipranavir + Ritonavir | Pro-140 |
| FLG | Nevirapine | Tipranavir + Ritonavir | PRO-542 |
| FLG | Nevirapine | Tipranavir + Ritonavir | SCH-D |

- 39 -

| | | | |
|-----|------------|---------------------------|------------|
| FLG | Nevirapine | Tipranavir + Ritonavir | TAK-220 |
| FLG | Nevirapine | Tipranavir + Ritonavir | TNX-355 |
| FLG | Nevirapine | Tipranavir + Ritonavir | UK-427,857 |

Table 5 illustrating combinations of a compound of the formula (I), nevirapine, a protease inhibitor, an integrase inhibitor and optionally one, two or more further NRTIs

5

| 1 st compound | 2 nd compound | 3 rd compound | 4 th compound |
|-----------------------------|-----------------------------|--------------------------|--------------------------|
| FLT | Nevirapine | Amprenavir | L-870810 |
| FLT | Nevirapine | Amprenavir | c-2507 |
| FLT | Nevirapine | Amprenavir | S(RSC)-1838 |
| FLT | Nevirapine | Atazanavir | L-870810 |
| FLT | Nevirapine | Atazanavir | c-2507 |
| FLT | Nevirapine | Atazanavir | S(RSC)-1838 |
| FLT | Nevirapine | Indinavir Sulfate | c-2507 |
| FLT | Nevirapine | Indinavir Sulfate | S(RSC)-1838 |
| FLT | Nevirapine | Indinavir Sulfate | L-870810 |
| FLT | Nevirapine | Lexiva | c-2507 |
| FLT | Nevirapine | Lexiva | L-870810 |
| FLT | Nevirapine | Lexiva | S(RSC)-1838 |
| FLT | Nevirapine | Lopinavir + Ritonavir | L-870810 |

- 40 -

| | | | |
|-----|------------|------------------------|-------------|
| FLT | Nevirapine | Lopinavir + Ritonavir | c-2507 |
| FLT | Nevirapine | Lopinavir + Ritonavir | S(RSC)-1838 |
| FLT | Nevirapine | Nelfinavir Mesylate | L-870810 |
| FLT | Nevirapine | Nelfinavir Mesylate | c-2507 |
| FLT | Nevirapine | Nelfinavir Mesylate | S(RSC)-1838 |
| FLT | Nevirapine | Ritonavir | L-870810 |
| FLT | Nevirapine | Ritonavir | c-2507 |
| FLT | Nevirapine | Ritonavir | S(RSC)-1838 |
| FLT | Nevirapine | Saquinavir | L-870810 |
| FLT | Nevirapine | Saquinavir | c-2507 |
| FLT | Nevirapine | Saquinavir | S(RSC)-1838 |
| FLT | Nevirapine | Tipranavir + Ritonavir | L-870810 |
| FLT | Nevirapine | Tipranavir + Ritonavir | c-2507 |
| FLT | Nevirapine | Tipranavir + Ritonavir | S(RSC)-1838 |
| FLG | Nevirapine | Amprenavir | L-870810 |
| FLG | Nevirapine | Amprenavir | c-2507 |
| FLG | Nevirapine | Amprenavir | S(RSC)-1838 |
| FLG | Nevirapine | Atazanavir | L-870810 |
| FLG | Nevirapine | Atazanavir | c-2507 |
| FLG | Nevirapine | Atazanavir | S(RSC)-1838 |
| FLG | Nevirapine | Indinavir | c-2507 |

| | | Sulfate | |
|-----|------------|------------------------|-------------|
| FLG | Nevirapine | Indinavir Sulfate | S(RSC)-1838 |
| FLG | Nevirapine | Indinavir Sulfate | L-870810 |
| FLG | Nevirapine | Lexiva | c-2507 |
| FLG | Nevirapine | Lexiva | L-870810 |
| FLG | Nevirapine | Lexiva | S(RSC)-1838 |
| FLG | Nevirapine | Lopinavir + Ritonavir | L-870810 |
| FLG | Nevirapine | Lopinavir + Ritonavir | c-2507 |
| FLG | Nevirapine | Lopinavir + Ritonavir | S(RSC)-1838 |
| FLG | Nevirapine | Nelfinavir Mesylate | L-870810 |
| FLG | Nevirapine | Nelfinavir Mesylate | c-2507 |
| FLG | Nevirapine | Nelfinavir Mesylate | S(RSC)-1838 |
| FLG | Nevirapine | Ritonavir | L-870810 |
| FLG | Nevirapine | Ritonavir | c-2507 |
| FLG | Nevirapine | Ritonavir | S(RSC)-1838 |
| FLG | Nevirapine | Saquinavir | L-870810 |
| FLG | Nevirapine | Saquinavir | c-2507 |
| FLG | Nevirapine | Saquinavir | S(RSC)-1838 |
| FLG | Nevirapine | Tipranavir + Ritonavir | L-870810 |
| FLG | Nevirapine | Tipranavir | c-2507 |

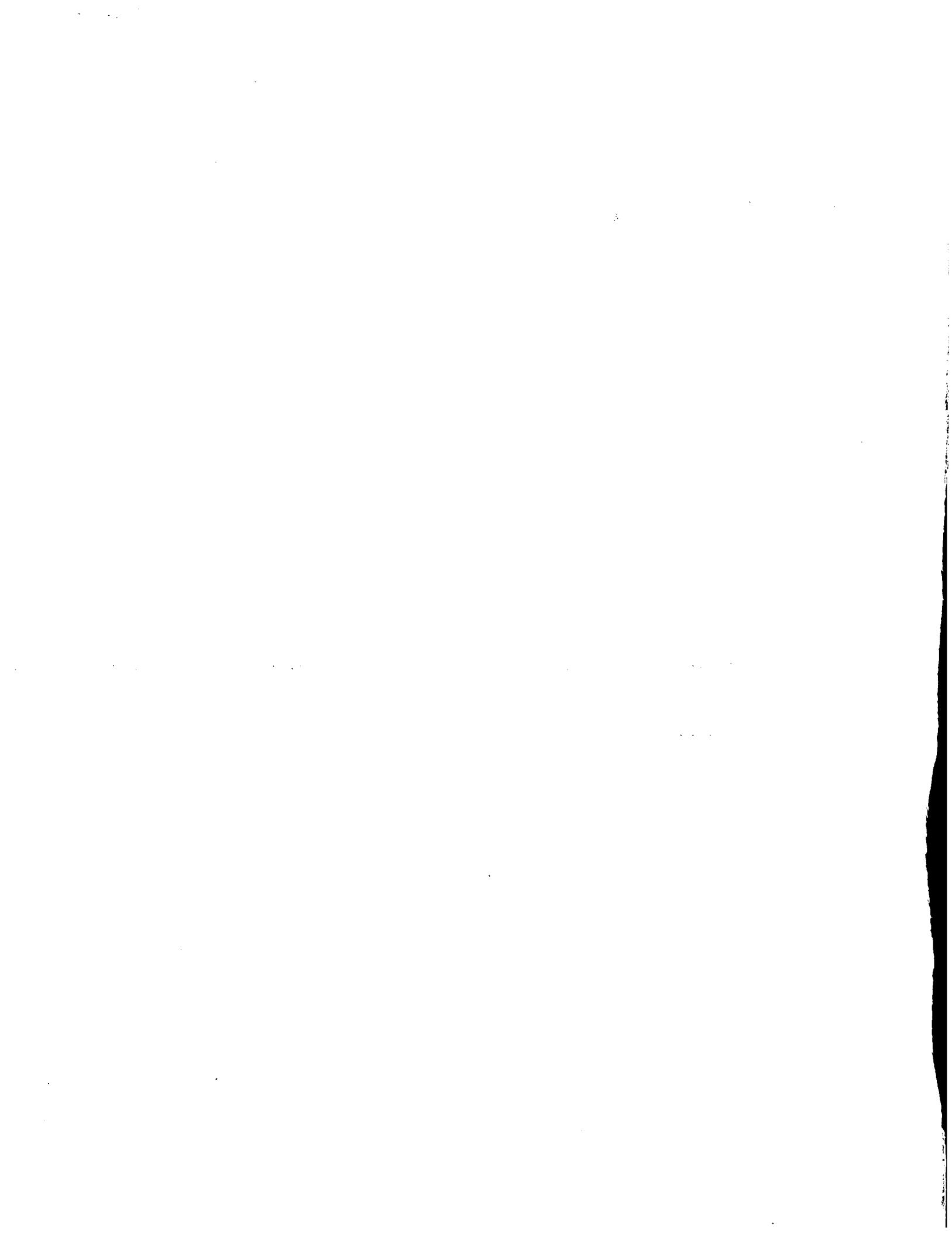
| | | | |
|-----|------------|---------------------------|-------------|
| | | + Ritonavir | |
| FLG | Nevirapine | Tipranavir + Ritonavir | S(RSC)-1838 |

Table 6 illustrating combinations of a compound of the formula (I), nevirapine and a further antiviral

| 1 st compound | 2 nd compound | 3 rd compound | 4 th compound |
|-----------------------------|-----------------------------|------------------------------|--------------------------|
| FLT | Nevirapine | PA-457 | |
| FLT | Nevirapine | KPC-2 | |
| FLT | Nevirapine | HGTB-43 | |
| FLT | Nevirapine | Delavirdine | |
| FLT | Nevirapine | Efavirenz | |
| FLT | Nevirapine | (+)- Calanolide A or B | |
| FLT | Nevirapine | Capravirine | |
| FLT | Nevirapine | GW-695634 | |
| FLT | Nevirapine | MIV-150 | |
| FLT | Nevirapine | MV026048 | |
| FLT | Nevirapine | NV-05 | |
| FLT | Nevirapine | R-278474 | |
| FLT | Nevirapine | RS-1588 | |
| FLT | Nevirapine | TMC-120/125 | |
| FLT | Nevirapine | TMC-125 | |
| FLT | Nevirapine | UC-781 | |
| FLT | Nevirapine | YM-215389 | |
| FLG | Nevirapine | PA-457 | |

| | | | |
|-----|------------|------------------------------|--|
| FLG | Nevirapine | KPC-2 | |
| FLG | Nevirapine | HGTB-43 | |
| FLG | Nevirapine | Delavirdine | |
| FLG | Nevirapine | Efavirenz | |
| FLG | Nevirapine | (+)- Calanolide A or B | |
| FLG | Nevirapine | Capravirine | |
| FLG | Nevirapine | GW-695634 | |
| FLG | Nevirapine | MIV-150 | |
| FLG | Nevirapine | MV026048 | |
| FLG | Nevirapine | NV-05 | |
| FLG | Nevirapine | R-278474 | |
| FLG | Nevirapine | RS-1588 | |
| FLG | Nevirapine | TMC-120/125 | |
| FLG | Nevirapine | TMC-125 | |
| FLG | Nevirapine | UC-781 | |
| FLG | Nevirapine | YM-215389 | |

In the above given Tables 1 to 6 the term "FLG" is 2',3'-dideoxy-3'-fluoroguanosine, or a pharmaceutically acceptable salt or prodrug thereof, in particular 3'-deoxy-3'-fluoro-5-O-
5 [2-(L-valyloxy)-propionyl]guanosine, or a pharmaceutically acceptable salt thereof.

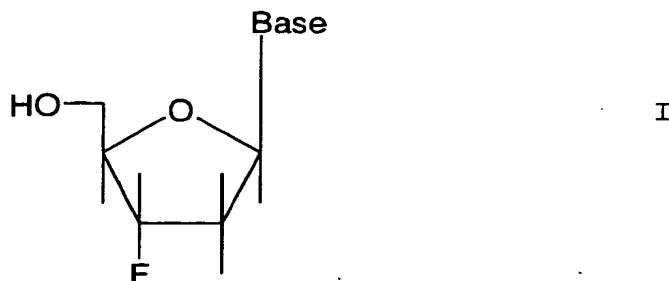


20. Dez. 2003

Claims:

1. A pharmaceutical composition useful for the treatment or prophylaxis of viral infections comprising nevirapine and at least one antiviral active compound of formula (I)

5



wherein Base is selected from the group consisting of thymine, cytosine, adenine, guanine, inosine, uracil, 5-ethyluracil and 2,6-diaminopurine, or a pharmaceutically acceptable salt or

10 prodrug thereof.

2. The pharmaceutical composition according to claim 1 wherein the compound of formula (I) is 3'-deoxy-3'-fluorothymidine, or a pharmaceutically acceptable salt or

15 prodrug thereof.

3. The pharmaceutical composition according to claim 1 wherein the compound of the formula (I) is FLG or a pharmaceutically acceptable salt or prodrug thereof, in particular 3'-deoxy-3'-fluoro-5-O-[2-(L-valyloxy)-propionyl]guanosine or a pharmaceutically acceptable salt thereof.

25 4. The pharmaceutical composition according to one or more of the claims 1 to 3 wherein nevirapine and the at least one compound of formula (I) are present in a synergistic ratio.

30 5. The pharmaceutical composition according to one or more of the claims 1 to 4 wherein nevirapine and the at least one compound of the formula (I) are present in a

- 45 -

ratio between about 1:250 to about 250:1.

6. The pharmaceutical composition according to claim 5 wherein nevirapine and the at least one compound of the formula (I) 5 are present in a ratio between about 1:50 to about 50:1.

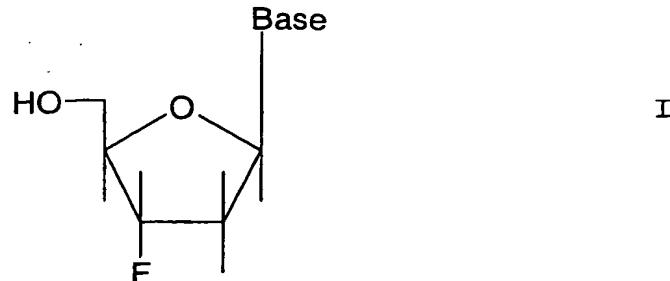
7. The pharmaceutical composition according to one or more of the claims 1 to 6 further comprising one, two or more further NRTI, or a pharmaceutically acceptable salt or prodrug 10 thereof.

8. The pharmaceutical composition according to claim 7 wherein (a) the compound of the formula (I) is 3'-deoxy-3'-fluorothymidine, or a pharmaceutically acceptable salt or 15 prodrug thereof, and the further NRTI is FLG or a pharmaceutically acceptable salt or prodrug thereof, in particular 3'-deoxy-3'-fluoro-5-O-[2-(L-valyloxy)-propionyl]guanosine or a pharmaceutically acceptable salt thereof, or
20 (b) the compound of the formula (I) is FLG or a pharmaceutically acceptable salt or prodrug thereof, and the further NRTI is 3'-deoxy-3'-fluorothymidine, or a pharmaceutically acceptable salt or prodrug thereof.

25 9. The pharmaceutical composition according to one or more of the claims 1 to 8 with at least one pharmaceutically acceptable carrier.

10. The pharmaceutical composition according to one or more of 30 the claims 1 to 9 for use in the treatment or prophylaxis of human retroviral (HRV) infections.

11. Use of nevirapine in combination or alternation with at least one antiviral active compound of formula (I)



I

wherein Base is selected from the group consisting of thymine, cytosine, adenine, guanine, inosine, uracil, 5-ethyluracil and 2,6-diaminopurine, or a pharmaceutically acceptable salt or 5 prodrug thereof, in the prophylaxis or treatment of a viral infection in a patient.

12. The use according to claim 11, wherein the compound of formula (I) is 3'-deoxy-3'-fluorothymidine, or a 10 pharmaceutically acceptable salt or prodrug thereof.

13. The use according to claim 11, wherein the compound of the formula (I) is FLG or a pharmaceutically acceptable salt or prodrug thereof, in particular 3'-deoxy-3'-fluoro-5-O-[2-(L-15 valyloxy)-propionyl]guanosine or a pharmaceutically acceptable salt thereof.

14. The use according to claim 11, 12 or 13 in the prophylaxis or treatment of a human retroviral infection (HRV) in a 20 patient.

15. The use according to one or more of the claims 11 or 14 in the prophylaxis or treatment of a multiresistant HIV infection in a patient.

25 16. The use according to one or more of the claims 11 to 15 for preventing perinatal transmission of a human retroviral (HRV) infection from mother to baby.

- 47 -

17. The use according to one or more of the claims 11 to 16, wherein nevirapine and the at least one compound of formula (I) are administered to the patient in combination or alternation in a synergistic ratio.

5

18. The use according to one or more of the claims 11 to 17, wherein nevirapine and the at least one compound of formula (I) are administered to the patient in combination or alternation in a ratio between about 1:250 to about 250:1.

10

19. The use according to claim 18, wherein nevirapine and the at least one compound of formula (I) are administered to the patient in combination or alternation in a ratio between about 1:50 to about 50:1.

15

20. The use according to one or more of the claims 11 to 19 in combination or alternation with one, two or more further NRTI, or a pharmaceutically acceptable salt or prodrug thereof.

20

21. The use according to claim 20 wherein

(a) the compound of the formula (I) is 3'-deoxy-3'-fluorothymidine, or a pharmaceutically acceptable salt or prodrug thereof, and the further NRTI is FLG or a pharmaceutically acceptable salt or prodrug thereof, in particular 3'-deoxy-3'-fluoro-5-O-[2-(L-valyloxy)-propionyl]guanosine or a pharmaceutically acceptable salt thereof, or

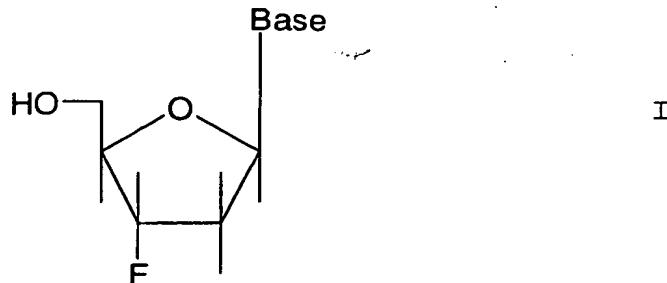
25

(b) the compound of the formula (I) is FLG or a pharmaceutically acceptable salt or prodrug thereof, and the further NRTI is 3'-deoxy-3'-fluorothymidine, or a pharmaceutically acceptable salt or prodrug thereof.

30

22. Use of nevirapine in combination with at least one antiviral active compound of formula (I)

35



wherein Base is selected from the group consisting of thymine, cytosine, adenine, guanine, inosine, uracil, 5-ethyluracil and 2,6-diaminopurine, or a pharmaceutically acceptable salt or

5 prodrug thereof, for the manufacture of a medicament for the prophylaxis or treatment of a viral infection in a patient.

23. The use according to claim 22, wherein the compound of formula (I) is 3'-deoxy-3'-fluorothymidine, or a
10 pharmaceutically acceptable salt or prodrug thereof.

24. The use according to claim 22, wherein the compound of the formula (I) is FLG or a pharmaceutically acceptable salt or prodrug thereof, in particular 3'-deoxy-3'-fluoro-5-O-[2-(L-
15 valyloxy)-propionyl]guanosine or a pharmaceutically acceptable salt thereof.

25. The use according to claim 22, 23 or 24, wherein nevirapine is used in combination with said compound of the formula (I) and one, two or more further NRTI, or a
20 pharmaceutically acceptable salt or prodrug thereof.

26. The use according to claim 25 wherein
(a) the compound of the formula (I) is 3'-deoxy-3'-
25 fluorothymidine, or a pharmaceutically acceptable salt or prodrug thereof, and the further NRTI is FLG or a pharmaceutically acceptable salt or prodrug thereof, in particular 3'-deoxy-3'-fluoro-5-O-[2-(L-valyloxy)-
propionyl]guanosine or a pharmaceutically acceptable salt
30 thereof, or

- 49 -

(b) the compound of the formula (I) is FLG or a pharmaceutically acceptable salt or prodrug thereof, and the further NRTI is 3'-deoxy-3'-fluorothymidine, or a pharmaceutically acceptable salt or prodrug thereof.

5

27. The use according to one or more of the claims 22 to 26 for the manufacture of a medicament for the prophylaxis or treatment of a human retroviral (HRV) infection in a patient.

10 28. The use according to one or more of the claims 22 to 27, wherein the medicament is a single dosage form.

29. The use according to one or more of the claim 22 to 27, wherein the medicament is a multiple dosage form.

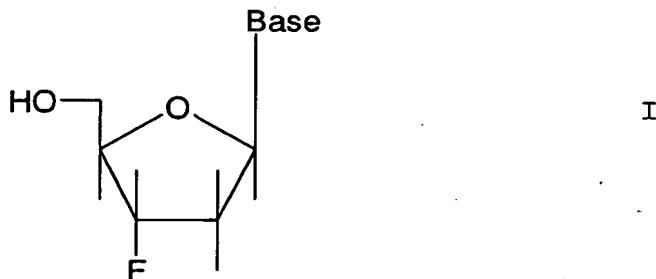
15

30. A kit of parts for the prophylaxis or treatment of a viral infection in a patient, comprising

(a) a first containment containing a pharmaceutical composition comprising nevirapine and at least one

20 pharmaceutically acceptable carrier, and

(b) a second containment containing a pharmaceutical composition comprising an antiviral active compound of formula (I)



25

wherein Base is selected from the group consisting of thymine, cytosine, adenine, guanine, inosine, uracil, 5-ethyluracil and 2,6-diaminopurine, or a pharmaceutically acceptable salt or prodrug thereof, and at least one pharmaceutically acceptable carrier.

30

- 50 -

31. The kit of parts according to claim 30, wherein the compound of formula (I) is 3'-deoxy-3'-fluorothymidine, or a pharmaceutically acceptable salt or prodrug thereof.

5

32. The kit of parts according to claim 30, wherein the compound of the formula (I) is FLG or a pharmaceutically acceptable salt or prodrug thereof, in particular 3'-deoxy-3'-fluoro-5-O-[2-(L-valyloxy)-propionyl]guanosine or a pharmaceutically acceptable salt thereof.

10

33. The kit of parts according to claim 30, 31 or 32 for use in the prophylaxis or treatment of a human retroviral (HRV) infection in a patient.

15

34. The kit of parts according to one or more of the claim 30 to 33 further comprising one, two or more further NRTI, or a pharmaceutically acceptable salt or prodrug thereof.

20

35. The kit of parts according to claim 34 wherein
(a) the compound of the formula (I) is 3'-deoxy-3'-fluorothymidine, or a pharmaceutically acceptable salt or prodrug thereof, and the further NRTI is FLG or a pharmaceutically acceptable salt or prodrug thereof, in particular 3'-deoxy-3'-fluoro-5-O-[2-(L-valyloxy)-propionyl]guanosine or a pharmaceutically acceptable salt thereof, or

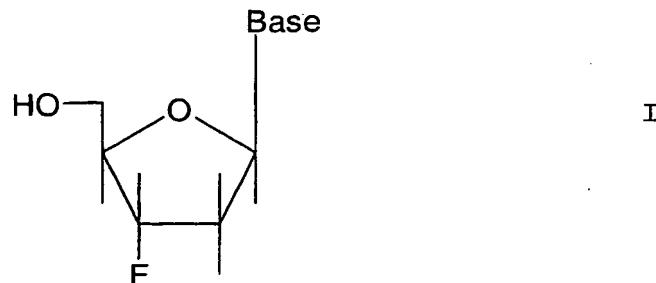
25

(b) the compound of the formula (I) is FLG or a pharmaceutically acceptable salt or prodrug thereof, and the further NRTI is 3'-deoxy-3'-fluorothymidine, or a pharmaceutically acceptable salt or prodrug thereof.

30

36. A manufacture comprising nevirapine and at least one antiviral active compound of formula (I)

35



wherein Base is selected from the group consisting of thymine, cytosine, adenine, guanine, inosine, uracil, 5-ethyluracil and 2,6-diaminopurine, or a pharmaceutically acceptable salt or 5 prodrug thereof, for use in combination or alternation in the prophylaxis or treatment of a viral infection in patient.

37. The manufacture according to claim 36, wherein the compound of formula (I) is 3'-deoxy-3'-fluorothymidine, or a 10 pharmaceutically acceptable salt or prodrug thereof.

38. The manufacture according to claim 36, wherein the compound of the formula (I) is FLG or a pharmaceutically acceptable salt or prodrug thereof, in particular 3'-deoxy-3'-fluoro-5-O-[2-(L- 15 valyloxy)-propionyl]guanosine or a pharmaceutically acceptable salt thereof.

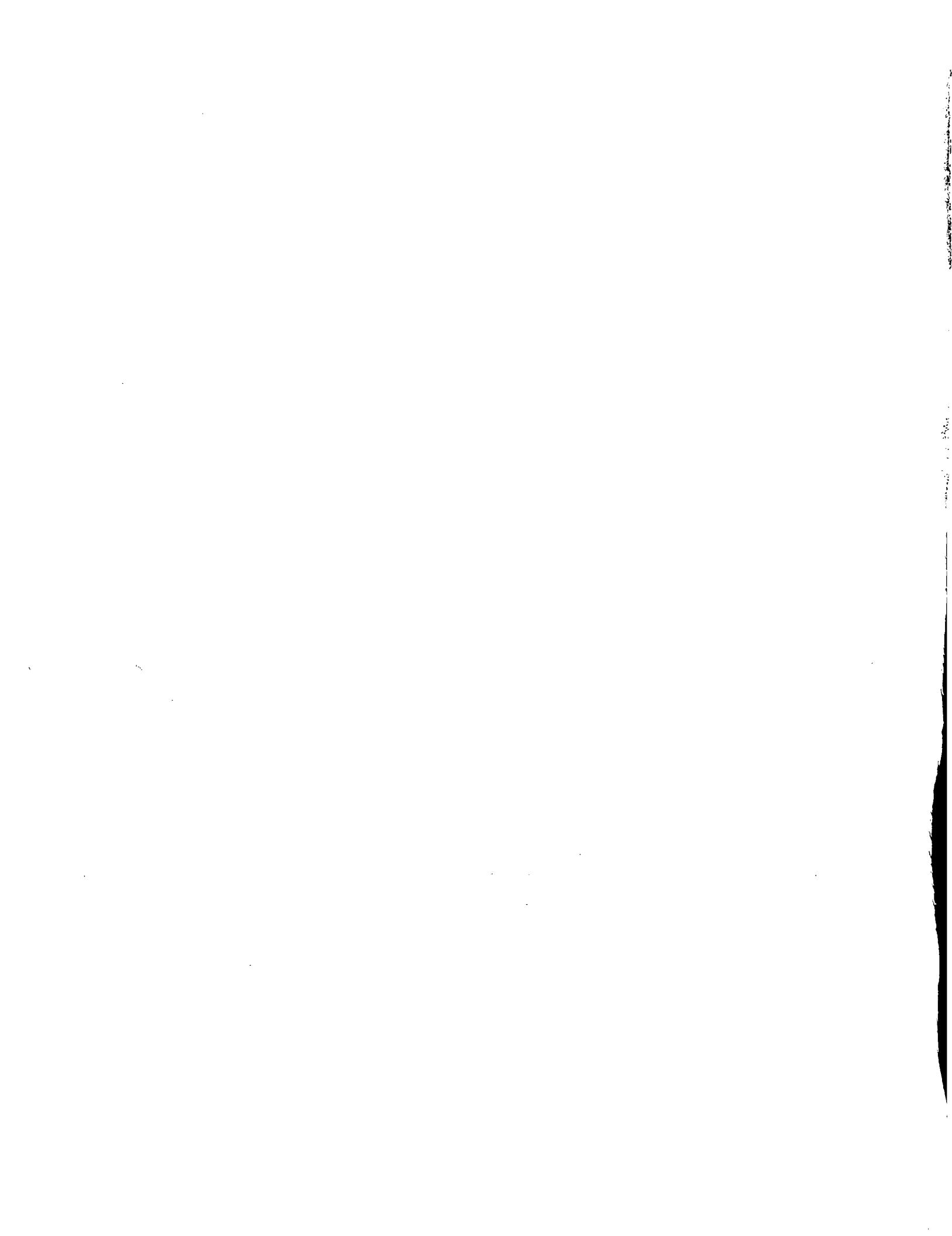
39. The manufacture according to claim 36, 37 or 38 for use in combination or alternation in the prophylaxis or treatment of a 20 human retroviral (HRV) infection in patient.

40. The manufacture according to one or more of the claims 36 to 39 further comprising one, two or more further NRTI, or a pharmaceutically acceptable salt or prodrug thereof.

25
41. The manufacture according to claim 40 wherein
(a) the compound of the formula (I) is 3'-deoxy-3'-fluorothymidine, or a pharmaceutically acceptable salt or prodrug thereof, and the further NRTI is FLG or a 30 pharmaceutically acceptable salt or prodrug thereof, in

particular 3'-deoxy-3'-fluoro-5-O-[2-(L-valyloxy)-propionyl]guanosine or a pharmaceutically acceptable salt thereof, or

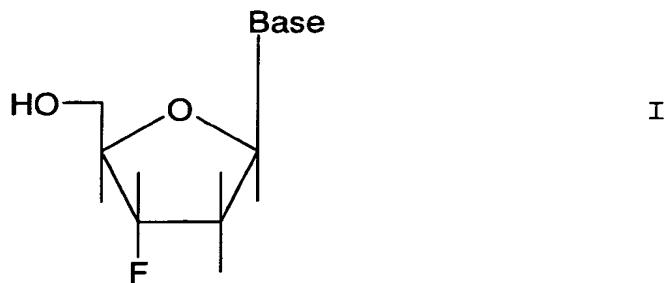
(b) the compound of the formula (I) is FLG or a
5 pharmaceutically acceptable salt or prodrug thereof, and the further NRTI is 3'-deoxy-3'-fluorothymidine, or a pharmaceutically acceptable salt or prodrug thereof.



20. Dez. 2003

Summary

In accordance with the present invention there is provided a pharmaceutical composition useful for the treatment or
5 prophylaxis of viral infections comprising nevirapine and at least one antiviral active compound of formula (I)



wherein Base is selected from the group consisting of thymine,
10 cytosine, adenine, guanine, inosine, uracil, 5-ethyluracil and 2,6-diaminopurine, or a pharmaceutically acceptable salt or prodrug thereof.

